On using fuzzy reinforcement learning to control the cancer cells

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Extended Abstract

Introduction: Chronic myelogenous (CML) is a cancer of the blood, and accounts for about 15% of all leukemia cases in adults. The median age for patients emerging CML is between 45 and 55 years, and one or two cases occur per 100000 people per year. Knowledge of Bcr-Abl as an abnormal tyrosine kinase protein has led to the invention of imatinib mesylate (known as Gleevec in the U.S. and henceforth mentioned to as imatinib). Prior to the development of imatinib, the most common chemotherapies used to treat CML included interferon-alpha, cytarabine and hydroxyurea, sometimes in combination. In this paper, we apply fuzzy reinforcement learning as a free model optimal controller to a CML model with a molecular targeted therapy (such as imatinib), and a broad cytotoxic chemotherapy (such as cytarabine). Our goal in this study is to minimize the cancer cell population and the disadvantageous effects of the two types of drugs to the body of a hypothetical individual. The action of these therapies is against broad classes of cells, and so treatment usually results in severe side effects. Several studies suggest that combination of imatinib with a broader chemotherapy has the potential to perform better than alone.

Fuzzy inference systems offer robust and smooth response. However, they do involve the existence of an expert to define the suitable rule-set. The main challenge is, therefore, to be able to make the appropriate rule-set without the existence of a direct trainer. Studies have been carried out to design fuzzy logic based controllers without the need of an expert's experience and information. To solve this issue Raju et al. proposed a fuzzy controller with the fuzzy sliding surface. Shao and Shihuang studied a fuzzy self-organizing controller, where the control policy is able to develop and improve by itself. Reinforcement learning (RL) can also be practical in this situation, to drive the generation of the suitable rule-set based on the interactions with the environment. It can be simply combined with fuzzy logic and provide the relationship between the states and the admissible action, which is the same as creating the fuzzy logic "if…then" engine. In this paper the approach of reinforcement learning is conducted toward having a real controller for reducing cancer cell population by using two different drugs dosages.

The rest of the paper was organized as follows. First of all the fuzzy reinforcement learning principles were considered. Then, mathematical model of cancer was introduced. Afterwards, this model was simulated in the MATLAB-SIMULINK environment. In the simulation section, the controller was implemented to the model. Finally, a comprehensive discussion concludes the paper.

Fuzzy-reinforcement learning strategy: Reinforcement Learning is a powerful tool for finding the optimum policy for a certain process. RL utilizes the environment feedback and produces a signal

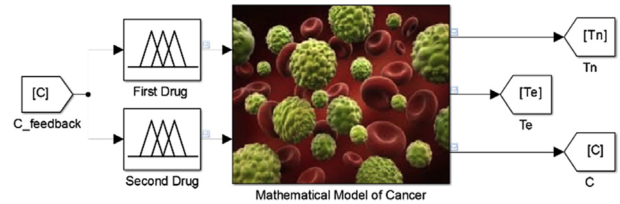

Fig. 1. Mathematical model and FRL controller in simulink environment.

named reinforcement. This signal might be a reward or a punishment. In an analogy to control systems, agent plays a same role as the process and action is as the controller signal. RL intention is to find the best action for each state which agent (process) wants to move to. Q-Learning is a simple algorithm which is used in this paper. This algorithm has a lookup table named Q table. It tries to estimate the discounted future rewards for taking actions from given states. This method is either impracticable in the case of large state-actions spaces, or impossible with continuous state spaces. Many studies proposed methods for approximating the Q table, these methods are not totally desirable because of their slow solution. Another approach is to integrate fuzzy sets and reinforcement learning together. In this case, all of states are the same as the inputs of fuzzy and action is defined as the output. Algorithm 1 shows the Q-Learning reinforcement learning principals with their equations. In this method, Takagi-Sugeno FIS is used and all of rules are between input membership functions, moreover, the constant outputs are tuned by Q-Learning.

- Observe the state x
- For each rule: choose the actual consequence using greedy or epsilon-greedy
- Compute the global consequence a(x) and its corresponding Q-value Q(x, a) by EQ. (2)
- Apply the action a(x) by EQ. (1). Let y be the new state
- Receive the reinforcement r
- Update Q-values by EQ3.(3-5)

Alg1. Q-Learning Reinforcement Learning Principals

$$a(x) = \left(\sum_{i=1}^{N} \alpha_i(X) \times a_i \right) \Bigg/ \sum_{i=1}^{N} \alpha_i(X)$$

$$Q(X,a) = \left(\sum_{i=1}^{N} \alpha_i(X) \times q\left[i.i^{\dagger}\right] \right) \Bigg/ \sum_{i=1}^{N} \alpha_i(X)$$

$$V(X) = \left(\sum_{i=1}^{N} \alpha_i(X) \times q\left[i.i^{*}\right] \right) \Bigg/ \sum_{i=1}^{N} \alpha_i(X)$$

$$\Delta Q = r + \gamma V(Y) - Q(X,a)$$

$$\Delta q\left[i.i^{\dagger}\right] = (\alpha \Delta Q)(\alpha_i(X)) / \sum_{i=1}^{N} \alpha_i(X)$$

In these equations, α is the learning rate, a is the action series, r is reinforcement, γ is discount rate and α_i is the truth value. The parameters mentioned in this algorithm are arbitrary and select by trial and error.

Modeling and simulation: The proposed mathematical model for cancer cells are employed from the research of Moore and Li

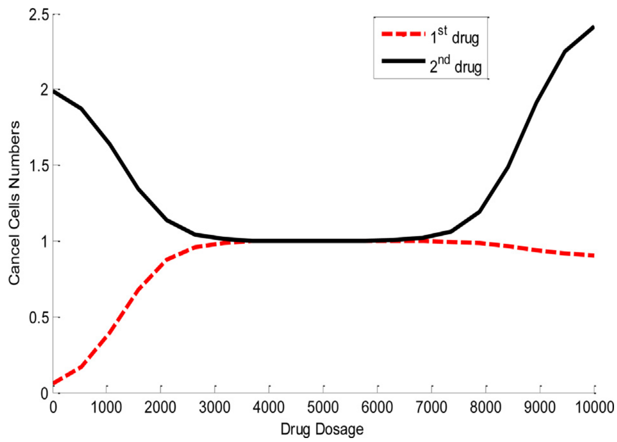

Fig. 2. Drug dosage policy determined from FRL algorithm.

in 2004. In this model as shown in (6), a set of differential equations are considered to show the growth of can cell population versus two mentioned drug dosages, u_1 as imatinib and u_2 as cytarabine.

$$\frac{dT_n}{dt} = s_n - u_2(t)d_nT_n - k_nT_n\left(\frac{C}{C+\eta}\right)$$
$$\frac{dT_e}{dt} = \alpha_n k_n T_n\left(\frac{C}{C+\eta}\right) + \alpha_e T_e\left(\frac{C}{C+\eta}\right) - u_2(t)d_eT_e - \gamma_e C T_e,$$
$$\frac{dC}{dt} = (1-u_1(t))r_c C \ln\left(\frac{C_{\max}}{C}\right) - u_2(t)d_c C - \gamma_c C T_e,$$

The proposed model was simulated in Simulink environment, where the fuzzy reinforcement learning controller is used. As shown in Figure 1, two controllers evaluated the dosage of drugs. After many iterations, fuzzy reinforcement learning presented a policy used for therapy as shown in Figure 2. By using this policy, the trend of drug dosage is shown in Figure 3. As illustrated in this graph, the dosage of the first drug, imatinib and the second one, cytarabine is decreased. It means the side effect of the drug considered in low level. Nevertheless, the cell population number is decreeing in Figure 4.

Conclusion: In this paper, a new free model based fuzzy reinforcement learning is introduced to meet the challenges of different patient conditions. In this method, a controller system is learned by some trial systematic therapies and finally make known to an expert therapist machine which can set the drug dosage for the proposed patient. Instead of a real patient, we used a mathematical model which determined the population of cancer cell for an special patient. By simulating the model in MATLAB-SIMULINK environment and employing the revealed controller, the achieved results show a reliably control by decreasing side effects.

Keywords: Reinforcement learning, Fuzzy logic, Cancer cells control, Mathematical model of cancer cell

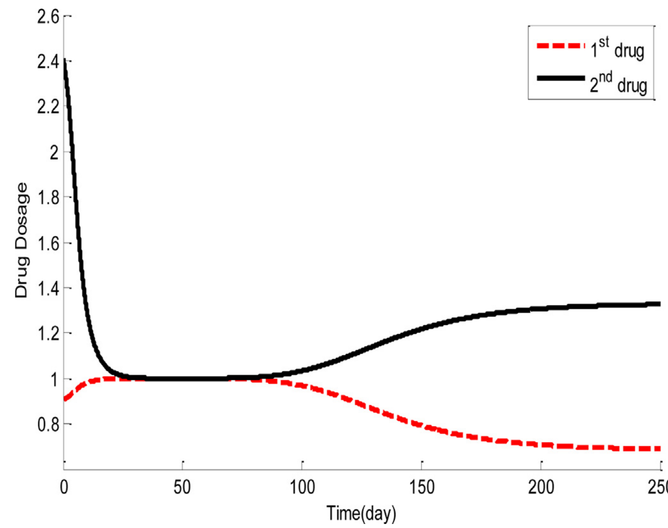

Fig. 3. Drug dosage used for the proposed patient.

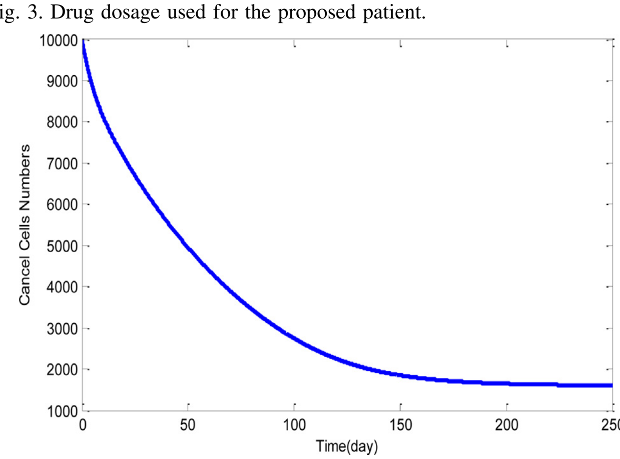

Fig. 4. Cancer population control versus time using FRL algorithm.

microRNA-124 overexpression in associated with lymph node metastasis in breast cancer

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Extended Abstract

Introduction: Breast cancer is the most frequent cancer and second most common cause of cancer related death in women worldwide. Although breast cancer is not a lethal cancer by self, metastasis to distant organs is the main cause of breast cancer mortality and is associated with poor prognosis in breast cancer patients. Spreading of tumor to auxiliary lymph node is one of the most important factors predicting metastasis of tumor cells. Conventional therapeutic strategies include assessment of local lymph node involvement

[1] Atieh Eslahi, Mahdieh Daliri Ghouchan Atigh contributed equally to this work.